Role of Novel Drug Delivery Systems in Stomach Specific Anti-Helicobacter Pylori Therapy

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ABSTRACT

Gastric cancer is the fourth most common cancer and the second leading cause of cancer-related death worldwide. In 1994, the International Agency for Research on Cancer classified Helicobacter pylori (H. pylori) as a class I (definite) carcinogen, as H. pylori infection is considered an important trigger in the process of carcinogenesis of both types of distal gastric cancer. Over the last decade, it has been widely reported that the success of H. pylori eradication treatment is falling. Over the last decade, it has been widely reported that the success of H. pylori eradication treatment is falling. Because conventional drug delivery systems do not remain in the stomach for prolonged periods, they are unable to deliver the antibiotics to the site of infection in effective concentrations and in fully active forms. It is therefore necessary to design drug delivery systems that cannot only alleviate the shortcomings of conventional delivery vehicles but also deliver the antimicrobials to the infected cell lines. To improve therapy against H. pylori infection by achieving bactericidal concentrations of antimicrobial agents in the stomach, novel formulations adhering to the gastric mucosa and releasing the drug at the site of infection would be significantly more effective than conventional systemically administered therapies. This review article discusses the role of novel drug delivery systems in stomach specific anti-Helicobacter Pylori Therapy.

Key words: Gastric cancer, H. pylori, Novel Drug Delivery System

INTRODUCTION

Gastric cancer is the fourth most common cancer and the second leading cause of cancer-related death worldwide. The estimated current incidence of gastric cancer is approximately 934,000 cases per year. In 1994, the International Agency for Research on Cancer classified Helicobacter pylori (H. pylori) as a class I (definite) carcinogen, as H. pylori infection is considered an important trigger in the process of carcinogenesis of both types of distal gastric cancer. H. pylori infection almost invariably causes chronic inflammation of the gastric mucosa. In the multistep process of carcinogenesis of intestinal type gastric carcinomas, chronic gastritis slowly progresses through the premalignant stages of atrophic gastritis, intestinal metaplasia and dysplasia into gastric adenocarcinoma. H. pylori infection is common worldwide. Generally, the prevalence is lower in developed countries than in developing countries.

Eradication guidelines

The Maastricht 2-2000 Consensus Report on the management of H. pylori recommends the use of proton pump inhibitors/ranitidine bismuth citrate (RBC) with clarithromycin and amoxycillin as First-line treatment in primary care. Second-line treatment after failure of the above therapy includes the use of proton pump inhibitors, bismuth, metronidazole, and tetracycline for a minimum of 7 days. If bismuth is not available, protonpump inhibitor-based triple therapy should be used for an extended period.

Eradication failure

Over the last decade, it has been widely reported that the success of H. pylori eradication treatment is falling. A steady decline was observed in the number of patients achieving eradication with standard first-line triple therapy of two antibiotics and a proton pump inhibitor. It now appears that the first-line eradication therapies most commonly used in everyday clinical practice fall considerably short of the 80% intention-to-treat (ITT) eradication rates that are considered the minimal acceptable levels as recommended in the Maastricht guidelines. It remains unclear how to re-treat patients after the failure of first-line therapy. Treatment failure sometimes leads to the development of bacterial resistance that makes it difficult to select a retreatment regimen.

Factors contributing to eradication failure

Recent biopsy studies and cell culture infection models have provided increasing evidence for the intracellular localization of H. pylori. Once acquired, H. pylori penetrates the gastric mucous layer and fixes itself to various phospholipids and glycolipids in the mucus gel. Therefore, access of antimicrobial drugs to the site is restricted from both the lumen of the stomach and the gastric blood supply. H. pylori may also acquire resistance to the commonly used antimicrobial agents. Because conventional drug delivery systems do not remain in the stomach for prolonged periods, they are unable to deliver the antibiotics to the site of infection in effective concentrations and in fully active forms. Also, many antimicrobial agents, such as penicillin and erythromycin, degrade rapidly in an acidic environment.

Above mentioned factors are one of the reason for failure of H. pylori eradication and also poor adherence to the eradication guidelines, cost, duration, and prevalence of bacterial resistance in certain geographical zones influence the H. pylori eradication.

Need of Novel drug delivery systems

It is therefore necessary to design drug delivery systems that cannot only alleviate the shortcomings of conventional delivery vehicles but also deliver the antimicrobials to the infected cell lines. The absorption of an antibiotic into the mucusthrough the mucus layer (from the gastric lumen) is believed to be more effective for H. pylori eradication than absorption through the basolateral membrane (from blood). A preparation that spreads out, adheres to the gastric mucosal surface, and continuously releases antibiotic should be highly effective against H. pylori.

To improve therapy against H. pylori infection by achieving bactericidal concentrations of antimicrobial agents in the stomach, novel formulations adhering to the gastric mucosa and releasing the drug at the site of infection would be significantly more effective than conventional systemically administered therapies.

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Novel drug delivery systems in H. pylori eradication therapy

Various mucoadhesive drug delivery systems have been proposed in H. pylori eradication, such as mucoadhesive microspheres, floating microspheres, microcapsules, magnetic systems, floating drug delivery systems, Swelling and Expandable Systems, Ion-Exchange resins and nanoparticles.

Mucoadhesive Systems

Mucoadhesion is a topic of current interest in the design of drug delivery systems. Mucoadhesive drug delivery system prolong the residence time of the dosage form at the site of application or absorption and facilitate an intimate contact of the dosage form with the mucosal surface and thus contribute to improved and/or better therapeutic performance of the drug. In recent years many such mucoadhesive drug delivery systems have been developed for H. pylori eradication.

Nagahara et al. formulated mucoadhesive microspheres containing amoxicillin. They dispersed the drug and bioadhesive polymers (carboxyvinyl polymer and curdlan in melted hydrogenated castor oil. They compared these microspheres with an amoxicillin suspension in infected Mongolian gerbils under feeding conditions. They concluded that the amoxicillin-microspheres provided 10 times greater anti-H. pylori activity than the amoxicillin suspension. Similarly Liu et al. also published a study on mucoadhesive microspheres containing amoxicillin. They prepared mucoadhesive microspheres by an emulsification/evaporation method, using ethylcellulose as matrix and carbopol 934P as a mucoadhesive polymer. Furthermore, they found a higher amoxicillin concentration in gastric tissue of rats after oral administration of mucoadhesive microspheres vs amoxicillin powder at the same dose. Finally, studies on the in vivo clearance of H. pylori revealed that, in a single-dosage administration (4 mg/kg to 14.8 mg/kg), the mucoadhesive microspheres had a better effectiveness. Katayama et al. proposed a sustained release liquid preparation using sodium alginate. In vitro, ampicillin release was retarded by calcium pre-treatment (0.10 M, 20 s) due to gel formation. To evaluate the gastric retention time of the preparation, the authors compared, in isolated perfused rat stomachs, the remaining percent of ampicillin when an aqueous ampicillin solution vs. the sodium alginate preparation were administrated. Hejazi and Amiji prepared tetracycline-loaded cross-linked chitosan microspheres prepared by ionic cross-linking and precipitation with sodium alginate. In vitro, tetracycline release was retarded by calcium pre-treatment (0.10 M, 20 s) due to gel formation. To evaluate the gastric retention time of the preparation, the authors compared, in isolated perfused rat stomachs, the remaining percent of ampicillin when an aqueous ampicillin solution vs. the sodium alginate preparation were administrated. Hejazi and Amiji prepared tetracycline-loaded cross-linked chitosan microspheres prepared by ionic cross-linking and precipitation with sodium alginate. In vitro, tetracycline release was retarded by calcium pre-treatment (0.10 M, 20 s) due to gel formation. To evaluate the gastric retention time of the preparation, the authors compared, in isolated perfused rat stomachs, the remaining percent of ampicillin when an aqueous ampicillin solution vs. the sodium alginate preparation were administrated.

Tokumura et al. prepared intra gastric buoyant sustained-release tablet containing amoxicillin by compressing the mixture of hydroxypropylcellulose-H, citric acid, sodium hydrogen carbonate. Chun et al. prepared Mucoadhesive microspheres containing either amoxicillin or clarithromycin via the interpolymer complexation of poly(acrylic acid) (PAA) with poly(vinyl pyrrolidone) (PVP) and solvent diffusion method. The drug release rate from the complex microspheres was significantly lower than that from the PVP microspheres. Ramteke et al. prepared and evaluated the oral mucoadhesive sustained release nanoparticles of clarithromycin. Clarithromycin containing gladiin nanoparticles were prepared by desolution method using pluronic F-68 as a stabilizing agent. Burgaz et al. prepared and evaluated clarithromycin containing mini-matrices by interpolymer complexes of chitosan and carboxymethylcellulose sodium salt.

Floating drug delivery systems

Floating drug delivery systems (FDDS) or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system.

Umamaehswari et al. developed polycarbonate microballoons by an emulsion (o/w) solvent evaporation technique. In vitro studies showed microballoons stayed buoyant up to 12 h and exhibited a sustained drug release profile. In vitro and in vivo growth inhibition studies were performed using cultures of H. pylori and H. pylori-infected Mongolian gerbils. Similarly they formulated floating bioadhesive microspheres consisting polycarbofih by an air-suspension coating method. In vitro floating studies, detachment force measurements and in vivo growth inhibition studies demonstrated the potential of this device, which combines bioadhesive and floating properties. Sahasathian et al. prepared and evaluated floating chitosan and alginate beads consisting amoxicillin. It showed excellent floating ability, high encapsulation efficiency, high drug loading capacity, and a strong in vitro mucoadhesion to the gastric mucosal layer. Yang et al. formulated a gas-generating system consisting of a expandable asymmetric triple layer tablet consisting of (poly(ethylene oxide), HPMC, sodium bicarbonate/calcium carbonate (poly(ethylene oxide), tetracycline hydrochloride and metronidazole. Jianhua Zheng et al. developed gastric floating-bioadhesive microparticles containing clarithromycin by a combined method of emulsification/evaporation and internal/ion gelation. In vivo mucoadhesive testing showed that 61% of the CAEMs could be retained in the stomach for 4 h.

Swelling and Expandable Systems

A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, three configurations are required, a small configuration for oral intake, an expanded gastroretentive form and a final unfolded system. Unfoldable systems are made of biodegradable polymer; the concept is to make a carrier, such as a capsule, incorporating a compressed system, which extends in the stomach. Swellable systems are also retained because of their mechanical properties. The swelling usually results from osmotic absorption of water. The dosage form is small enough to be swallowed, and swells in gastric liquids, the bulk enable gastric retention and maintains the stomach in a ‘fed’ state, suppressing housekeeper waves.

Muralidhar et al. developed the hydrodynamically balanced delivery system of Clarithromycin which, after oral administration should have the ability to prolong gastric residence time with the desired in vitro release profile for the localized action in the stomach, in the treatment of H.pylori mediated peptic ulcer. By applying wet granulation technique they prepared floating tablets of Clarithromycin. In vivo radiographic studies suggest that the tablet has increased gastric residence time for the effective localized action of the antibiotic (Clarithromycin) in the treatment of H.pylori mediated peptic ulcer.

Drug delivery systems with specific interaction

Classical mucoadhesion, which relies on non-specific interpenetration of polymer chains and mucus, the lectin–sugar interaction may represent a step forward towards epithelial drug delivery. Provided that the lectin-grafted drug delivery system can penetrate the mucus layer, the carbohydrate layer surrounding each mammalian cell represents a second target. “Cytoadhesion,” this concept is specifically based on certain materials that can reversibly bind to cell surfaces in the GIT. This next generation of mucoadhesives function with greater specificity because they are based on receptor-ligand-like interactions in which the molecules bind strongly and rapidly directly onto the mucosal cell surface rather than the mucus itself. One such class of compounds that has these unique requirements are called lectins.

Jain et al. formulated Lectin conjugated gastroretentive multiparticulate delivery system of clarithromycin for the effective treatment of H. pylori.
They developed and characterized a concanavalin-A conjugated gastroretentive multiparticulate delivery system of clarithromycin for the effective treatment of colonization of *H. pylori*. Ethylcellulose microspheres containing clarithromycin were prepared using emulsification/evaporation method. Performance of developed formulation in GI tract was visualized by gamma scintigraphy in rabbits. Prolonged gastric residence time of over 6 h was achieved in all rabbits for Con-A conjugated microspheres of clarithromycin. They concluded that designed targeted delivery system could possibly treat the colonization of *H. pylori*. Umamaheshwari et al. developed various formulations using lectins for *H. pylori* eradication.

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7. El-Shoura SM. Ethylcellulose microspheres containing clarithromycin were prepared using emulsification method. The amount of CAB-coated cholestyramine microcapsules that remained in the stomach was slightly lower than that of uncoated resin particles. Cholestyramine microcapsules were distributed throughout the stomach and exhibited prolonged gastric residence via mucoadhesion. They suggest that CAB-coated microcapsules could be a floating as well as a mucoadhesive drug delivery system. Thus, it has promise in the treatment of *H. pylori*. Burton et al. formulated Intragastric distribution of ion-exchange resins consisting of 99mTc-labelled cholestyramine. They suggest that oral dose forms containing finely-divided ion-exchange resins may form a useful system for topical treatment of the *H. pylori* infection.

**Nanoparticles**

Nanoparticle systems possess desirable features for treatment, including: (i) sustained and controlled release of drugs locally, (ii) potential to cross the mucosal barrier due to the nanometric size, (iii) rapid intracellular trafficking to the perinuclear region of underlying cells, and (iv) protection of cargo therapeutics from degradation and removal in the mucus. They have prepared clarithromycin- and omeprazole-containing gliadin nanoparticles with desolvation methods using pluronic F-68 as a stabilizing agent. Gliadin defines a group of polymorphic proteins extracted from gluten that are soluble in an ethanolic solution and show a remarkably low solubility in water, except at extreme pH. Due to these physicochemical properties, gliadin nanoparticles can be prepared by desolvation methods for macromolecules using environmentally acceptable solvents such as ethanol and water. These macromolecules showed a high capacity for drug loading and were soluble without further chemical or physical crosslinking. A complete study of pH-responsive chitosan/heparin nanoparticles for stomach-specific anti-*H. pylori* therapy was performed by Lin et al. In this study, pH-responsive nanoparticles were produced instantaneously upon the addition of a heparin solution to a chitosan solution with magnetic stirring at room temperature. The nanoparticles appeared to have a particle size of 130–300 nm, with a positive surface charge, and were stable at pH 1.2–2.5, allowing them to protect the incorporated amoxicillin from destructive gastric acids. Through in vivo studies, they demonstrated that the prepared nanoparticles adhered to and infiltrated cell–cell junctions and interacted locally with *H. pylori* infection sites in intercellular spaces.

**CONCLUSION**

To develop an efficient gastroretentive dosage form is a real challenge. Indeed, the drug delivery system must remain for a sufficient time in the stomach, which is not compatible with its normal physiology. Among all the dosage forms described herein, some provide interesting solutions, although many of them present drawbacks. In the particular case of *H. pylori* eradication, the ideal dosage form should, to be really effective, not only stay in the stomach, but also target the bacteria. Dosage form against *H. pylori* effective, if the dosage form designed based on *H. pylori* pathogenicity mechanisms.


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